Br Heart J 1981; **45**: 628–36

Effects of acute and chronic beta-receptor blockade on ventricular repolarisation in man*

NILS EDVARDSSON, S BERTIL OLSSON

From the Department of Cardiology, Medical Clinic I, Sahlgrenska Hospital, Göteborg, Sweden

SUMMARY The right ventricular repolarisation phase was studied electrophysiologically after an injection of 15 mg metoprolol in 16 healthy volunteers. Eight of them were restudied after chronic treatment with 400 mg metoprolol daily for five weeks. The assessment of the repolarisation time included ventricular effective refractory periods, monophasic action potential duration, and the QT interval measured during atrial stimulation at different driving frequencies. The acute administration of 15 mg metoprolol intravenously had no detectable effect on the repolarisation phase, while chronic treatment caused a significant increase of the ventricular effective refractory periods, monophasic action potential duration, and the QT interval during atrial stimulation. Thus the study confirmed the contrasting effect of acute and chronic beta-receptor blockade on the ventricular repolarisation time in man.

In the classification of antiarrhythmic drugs proposed by Vaughan Williams,[1] class II was reserved for the sympathicolytic agents. By interfering with the effects of catecholamines, beta-adrenergic blocking drugs reduce in vitro the slope of the phase 4 depolarisation of pacemaker cells within the sinus node, atria, atrioventricular node, and Purkinje fibres.

The effects on atrial muscle cells, Purkinje fibres, and ventricular muscle cells are generally small except in conditions with a high degree of sympathetic stimulation.[2] Beta-adrenergic receptor blocking drugs cause a decrease in the conduction velocity within the atria, atrioventricular node, Purkinje fibres, and ventricular myocardial cells, while there is little or no influence on the repolarisation time after acute administration.[3 4]

Some beta-adrenergic receptor antagonists, such as propranolol and alprenolol, also have a direct membrane-stabilising action, leading to delay of the depolarisation phase. This class I effect[1] is a pharmacological phenomenon seen in vitro at high concentrations and is not likely to be of any antiarrhythmic importance with therapeutic beta-blocking doses in a normally oxygenated muscle.[5–7]

Furthermore, recent studies in vitro on rabbit hearts showed that chronic beta-receptor blockade with propranolol, acebutolol, and practolol produced a slowly developing prolongation of the repolarisation time in both atria and ventricles. After two weeks a plateau level was reached and was sustained throughout the six-week period of treatment and for about two weeks after its discontinuation.[8 9]

This study was designed to determine whether a similar effect is obtained after chronic beta-receptor blockade in man, using the method of monophasic action potential recording.

Subjects and methods

Sixteen healthy young volunteers, all men (mean age 30 years, range 20 to 35 years) underwent an electrophysiological investigation and eight of them were also subjected to a second identical investigation after five weeks of oral beta-blockade (Fig 1).

The study was approved by the ethical committee of the University of Göteborg. Informed consent was obtained from each volunteer. None of them were taking any drugs at the time of the study.

Before the invasive part of the study a routine investigation was performed, including a medical history and a physical examination, laboratory tests, and a 12-lead electrocardiogram. All volunteers also had a chest *x*-ray film.

CATHETERISATION PROCEDURE

Under local anaesthesia, a bipolar pacemaker electrode catheter was introduced percutaneously via the right femoral vein into the right atrium,

*This study was supported by grants from the Medical Society of Göteborg and The National Society Against Heart and Chest Diseases.

Received for publication 31 July 1980

where atrial stimulation for QT interval studies was performed laterally in the vicinity of the sinuatrial node. The catheter was then repositioned for recording of the His bundle electrogram and then into a stable position at the right ventricular apex.

A bipolar suction electrode catheter for recording of monophasic action potential signals was then also introduced percutaneously via the right femoral vein and placed across the tricuspid valve in a non-arrhythmogenic position.

The ventricular effective refractory period was determined through the pacemaker electrode at the apex, and the suction electrode catheter tip was then carefully placed perpendicular to the endocardial wall in the outflow tract, and suction (−350 mmHg) was applied. A simultaneously recorded normal right ventricular electrogram was required for the monophasic action potential signal to be accepted.

After the signals had been recorded the ventricular effective refractory period was determined by stimulating through the suction electrode catheter during maintenance of suction. Thus, the position was identical to that from which the monophasic action potential signals had been obtained. Care was taken not to exceed a continuous suction time of two minutes.

When these measurements were concluded, 15 mg metoprolol was given intravenously over a period of five minutes. Blood pressure and heart rate were checked before, during, and after the injection at two-minute intervals. Ten minutes after the end of the injection all measurements were repeated in the reverse order.

Great care was taken to keep the pacemaker electrode in an unchanged position during all measurements and the monophasic action potential catheter in a fluoroscopically identical position, though suction had to be released between the recordings.

Blood samples for analysis of the concentration of metoprolol in plasma were collected immediately before and 10 minutes after the injection.

TECHNICAL EQUIPMENT

A 5 F USCI bipolar electrode catheter (USCI International Cat. No. 007150) was used for His bundle electrogram recording and for atrial and ventricular stimulation.

A special bipolar suction electrode catheter (ABO Trading, Kullavik, Sweden) enabled the right ventricular monophasic action potential and right ventricular electrogram to be recorded simultaneously. The technique of monophasic action potential recording has been extensively described elsewhere.[10 11]

The praecordial electrocardiogram lead V2, the His bundle electrogram, the monophasic action potential signal, and the right ventricular electrogram were displayed on an oscilloscope (Philips) and on an FM tape recorder (Bell and Howell). The monophasic action potential signal was amplified with a DC coupled amplifier and a preamplifier with an input impedance of 10^{11} ohms. Proper reproduction was allowed between DC and 625 Hz on the tape recorder, including all parts of the monophasic action potential signal.

During the study the praecordial electrocardiogram, the His bundle electrogram, the monophasic action potential signal, and the right ventricular electrogram were also recorded on a Mingograf 82 (Siemens-Elema AB, Sweden), with a frequency response of DC-700 Hz, at a paper speed of 100 mm/s, but were afterwards replayed from the tape at 250 mm/s. The latter recordings were used for analysis of the data.

The pacemaker (Siemens-Elema AB, Sweden) produced square wave impulses of constant current with a duration of 2 ms. Twice the diastolic threshold was used for stimulation. Premature stimuli were released manually at a predetermined interval within a possible range of 100 to 1000 ms (± 1 ms) after a basic stimulus.

INDICES OF VENTRICULAR REPOLARISATION (Fig. 2)

The QT interval was calculated from lead V2.

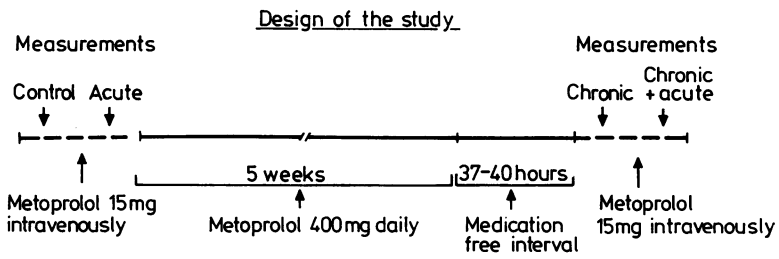

Fig. 1 *Design of the study. For further information, see text.*

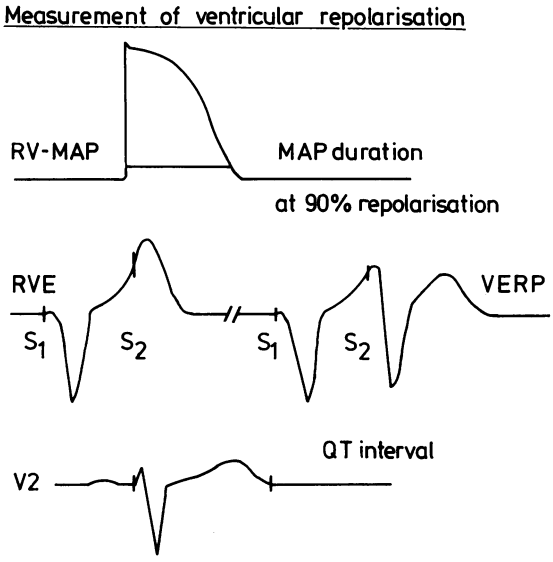

Fig. 2 *Measurement of ventricular repolarisation. MAP, monophasic action potential, the duration of which is measured at the level of 90 per cent repolarisation. VERP, ventricular effective refractory period; RVE, right ventricular electrogram. S_1, basic stimulus; S_2, early interpolated stimulus.*

Atrial pacing was performed in 30 s periods at basic cycle lengths of 670, 600, 545, and 500 ms. The last paced beat of each period was used for QT interval measurements.

QTc was calculated according to the Bazett formula[12] from the QT interval during spontaneous sinus rhythm.

The effective refractory periods of the right ventricular apex and outflow tract were estimated by means of programmed ventricular stimulation.[13–15] Single premature impulses were released after every eighth paced ventricular beat at increasing intervals until a propagated ventricular response occurred. The longest interval between the basic and the premature stimulus that did not produce a propagated response was taken as the effective refractory period.

Monophasic action potentials were recorded from the right ventricular outflow tract during sinus rhythm and during ventricular stimulation at a basic cycle length of 500 ms. The monophasic action potential duration at 90 per cent repolarisation was calculated.[11]

SECOND INVESTIGATION

Eight volunteers started oral metoprolol treatment with a dose of 200 mg twice daily immediately after

Table 1 *Heart rate, QT interval during sinus rhythm, QTc and QT interval during atrial stimulation*

Case No.	*Age (y)*	*Heart rate/min* C	A	Ch	Ch+A	*QT Sinus rhythm* C	A	Ch	Ch+A	*QTc Sinus rhythm* C	A	Ch	Ch+A	*QT bcl 670 ms* C	A	Ch	Ch
1	28	71	58	62	56	0·38	0·38	0·395	0·440	0 39	0 36	0·44	0·42	0 365	0·38	0 38	0 4(
2	32	58	45	54	52	0·415	0·43	0·445	0·435	0·41	0 39	0·42	0 39	0·375	0·38	0·39	0 3(
3	24	72	63	60	58	0·365	0·375	0·415	0·41	0·42	0·40	0·42	0·41	0 37	0·365	0·385	0 3(
4	34	77	66	71	66	0·375	0·385	0·405	0·410	0·44	0·41	0 45	0·43	—	0·37	0 385	0 3(
5	33	55	54	55	52	0·40	0·40	0·405	0·385	0·41	0 42	0 40	0 39	0 36	0·36	0·365	0 3(
6	33	62	51	59	51	0·42	0·425	0·425	0·435	0·43	0 39	0·40	0·41	0·375	0 38	0·38	0 3(
7	31	67	66	60	54	0·395	0 385	0·415	0·42	0·41	0·40	0·42	0 39	0·36	—	0·375	0 3(
8	25	78	60	70	61	0·400	0·410	0·405	0·40	0·41	0·42	0·45	0·42	0 375	0 385	0·38	0 3(
1–8 Mean	30	68	58	61	56	0·394	0·399	0·414	0·416	0·415	0 398	0·425	0·408	0·369	0·376	0 380	0 3(
SD		9	7	6	5	0·019	0·021	0·016	0·020	0·015	0·02	0·02	0 016	0·007	0·009	0·008	0 0(
		p<0·01		p<0·001		p<0·01				p<0·05		p<0·01		p<0·01			
		p<0·01				p<0·05				p<0·05				p<0·001			
		p<0·001				p<0·05										p<0·02	
9	30	65	57			0·39	RBBB			0·41	RBBB			0·355	RBBB		
10	30	60	55			0·41	0·41			0·42	0·39			0·38	0·39		
11	34	66	50			0·41	0·41			0·41	0·37			0·37	0·38		
12	20	64	62			0·39	0·41			0·42	0·39			0·38	0·40		
13	22	85	69			0·395	0·39			0·43	0·43			0·365	0·38		
14	35	63	54			0·385	0·39			0·385	0·37			0·34	0·35		
15	35	56	46			0·415	0·38			0·39	0·39			0·385	0·385		
16	33	63	56			0·41	0·41			0·41	0·40			0·385	0·38		
1–16 Mean	30	66	57			0·397	0·400			0·412	0·395			0·369	0·378		
SD		8	7			0·016	0·017			0·015	0·020			0·012	0·013		
		p<0·001								p<0·01				p<0·02			

C, control; A, acute effects of first injection; Ch, chronic treatment; Ch + A, acute effects of second injection after chronic treatment; RBBB, ri bundle-branch block; bcl, basic cycle length. (QT and QTc values are given in seconds.) *Note:* Cases 9 to 16 underwent the acute part of the st only, which is why there are no data after chronic treatment.

the first catheterisation. After five weeks the treatment was stopped and 36 to 40 hours later a second catheterisation was performed, in exactly the same way as the first one. The drug-free interval before the second study was assumed to allow the plasma concentration of metoprolol to decrease to zero.

STATISTICAL METHODS

For the statistical analysis of the data Student's t test for paired differences was used. The level of statistical significance was $p < 0.05$, but for additional information all actual p values are given. Comparisons of the acute effects have been made in all 16 volunteers, while the eight volunteers undergoing chronic treatment have been compared in respect of both acute and chronic effects.

Results

HEART RATE (Table 1)

The heart rate decreased after an acute injection of metoprolol both in untreated volunteers ($p < 0.001$) and after chronic treatment ($p < 0.001$). After five weeks of oral treatment the heart rate was still lower than before treatment ($p < 0.001$).

QTc (Table 1)

QTc was calculated from the QT interval during sinus rhythm. After an injection of metoprolol QTc decreased both in untreated ($p < 0.05$) and chronically treated volunteers ($p < 0.01$). Chronic treatment did not cause any significant change.

QT INTERVAL DURING ATRIAL STIMULATION (Table 1, Fig. 4)

The QT interval shortened as a result of increasing paced heart rate. Chronic metoprolol treatment, however, produced a small, consistent, and significant increase in the QT interval at each paced cycle length compared with the control recordings ($p < 0.01$).

AH INTERVAL (Table 2)

Intranodal conduction time, as measured from the AH interval in the His bundle electrogram, increased after the first injection in the untreated volunteers, while there were no changes after chronic treatment or after an additional injection in chronically treated subjects.

HQ INTERVAL (Table 2)

The infranodal conduction time was estimated from the HQ interval in the His bundle electrogram. No changes were seen at any time.

QT bcl 600 ms				*QT bcl 545 ms*				*QT bcl 500 ms*			
?	*A*	*Ch*	*Ch+A*	*C*	*A*	*Ch*	*Ch+A*	*C*	*A*	*Ch*	*Ch+A*
·35	0·37	0·37	0·39	0·345	0·36	0·36	0·38	0·335	0·345	0·33	0·36
·37	0·375	0·39	—	0·36	0·375	0·375	0·37	0·35	0·355	0·36	0·36
·36	0·36	0·39	0·40	0·36	0·36	0·385	—	0·35	—	0·38	—
·36	0·36	0·37	0·385	0·36	0·35	0·37	0·375	0·35	0·34	0·36	0·36
·35	0·35	0·35	0·35	0·335	0·33	0·335	0·35	0·335	0·33	0·325	0·34
·365	0·37	0·37	0·38	0·35	0·35	0·36	0·37	0·34	0·34	0·34	0·36
·34	—	0·36	0·37	0·34	—	0·345	0·355	0·325	—	0·33	0·34
·38	0·37	0·36	0·365	0·345	0·36	0·35	0·35	0·345	0·355	0·34	0·34
·359	0·365	0·370	0·377	0·349	0·355	0·360	0·364	0·341	0·344	0·346	0·351
·013	0·009	0·014	0·017	0·010	0·014	0·016	0·012	0·009	0·010	0·019	0·011
	$p < 0.01$				$p < 0.01$				$p < 0.05$		
	$p < 0.05$				$p < 0.01$				$p < 0.02$		
	$p < 0.01$										
·355	RBBB			0·35	RBBB			0·33	RBBB		
·375	0·37			0·355	0·36			0·35	0·36		
·36	0·38			0·335	0·36			0·33	0·35		
·37	—			0·37	—			—	—		
·36	0·36			0·35	0·35			0·34	0·33		
·33	0·335			0·325	0·33			0·31	0·33		
·38	0·38			0·375	—			—	—		
·37	0·37			0·36	—			0·34	—		
·361	0·365			0·351	0·353			0·338	0·344		
·014	0·012			0·013	0·013			0·012	0·011		

Table 2 *Intranodal conduction (AH interval), infranodal conduction (HQ interval), ventricular effective refractory periods (VERP), right ventricular monophasic potential duration (RV-MAP), and VERP/MAP ratio at right ventricular outflow tract*

Case No.	AH (ms)				HQ (ms)				VERP-apex (ms) bcl 500 ms				VERP-ot (ms) bcl 500 ms				RV-MAP (ms) bcl 500 ms			
	C	A	Ch	Ch + A	C	A	Ch	Ch + A	C	A	Ch	Ch + A	C	A	Ch	Ch + A	C	A	Ch	C
1	110	120	120	115	55	50	50	55	220	232	242	244	210	240	240	254	260	260	265	2
2	70	70	75	80	40	40	40	40	240	240	262	254	230	230	260	240	250	280	280	2
3	75	100	100	120	55	50	45	45	220	224	250	244	222	222	262	292	230	225	280	2
4	80	100	75	100	45	45	35	40	230	228	254	240	220	222	250	212	230	240	260	2
5	120	120	110	115	40	40	45	45	232	234	230	234	240	234	224	252	255	255	265	2
6	75	80	55	60	45	40	40	45	234	240	250	240	214	230	240	250	280	290	280	2
7	140	195	100	100	30	30	40	40	230	230	232	242	220	240	240	250	245	240	255	2
8	70	80	80	90	50	45	45	50	240	242	250	244	232	220	264	274	266	260	260	2
1-8 Mean	93	108	89	98	45	43	43	45	231	234	246	243	224	230	248	253	252	256	268	2
SD	27	40	22	20	8	7	5	5	8	6	11	6	10	8	14	23	17	22	10	
	p<0·05		NS		NS		NS		p<0·02				p<0·01				p<0·05			
									p<0·01				p<0·05				p<0·01			
									p<0·02				p<0·02				p<0·01			
									p<0·01				p<0·05							
9	90	100			55	50			242	232			220	240			240	240		
10	90	130			50	50			234	230			232	222			250	245		
11	100	110			50	50			234	234			228	240			270	260		
12	90	90			40	45			224	230			222	212			240	240		
13	80	100			45	40			230	234			242	204			230	220		
14	75	100			55	55			230	240			234	232			265	270		
15	120	140			50	55			232	222			240	232			265	230		
16	120	120			50	50			240	242			262	230			265	270		
1-16 Mean	94	110			47	46			232	233			229	228			253	252		
SD	22	30			7	7			7	6			13	11			16	20		
	p<0·01				NS				NS				NS				NS			

C, control; A, acute effects of first injection; Ch, chronic treatment; Ch + A, acute effects of second injection after chronic treatment; bcl, basic c length; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Note: Cases 9 to 16 underwent only the acute part of the study which is why there are no data after chronic treatment.

VENTRICULAR EFFECTIVE REFRACTORY PERIODS (Table 2)

The ventricular effective refractory period behaved similarly at the apex and in the outflow tract. No significant change was seen after the injections, either in untreated or in chronically treated volunteers. Chronic treatment, on the other hand, produced a moderate prolongation of the ventricular effective refractory period at the apex ($p < 0.01$) and in the outflow tract ($p < 0.01$).

MONOPHASIC ACTION POTENTIAL DURATION (Table 2)

The monophasic action potential duration at 90 per cent repolarisation did not change after the injections of metoprolol. Chronic treatment, however, caused an increase in the monophasic action potential duration ($p < 0.05$) compared with that before treatment (Fig. 3).

VENTRICULAR EFFECTIVE REFRACTORY PERIOD/MONOPHASIC ACTION POTENTIAL DURATION (VERP/MAP RATIO) (Table 2)

The VERP/MAP ratio, calculated from the same recording site in the outflow tract, showed no changes. After chronic treatment the ratio increased in five volunteers, decreased in two, and remained unchanged in one. An additional intravenous injection of metoprolol increased the ratio in five and decreased it in three subjects.

PLASMA CONCENTRATION OF METOPROLOL (Table 2)

As expected, the plasma concentration 36 to 40 hours after withdrawal of chronic treatment was zero. In one blood sample, however, a high unrealistic value was obtained. Reanalysis of the blood sample gave exactly the same result. Since the plasma concentration after an additional intravenous dose of metoprolol in this subject was considerably lower and within the expected range, the sample in question remains suspect, but the explanation is unsure. This sample value, shown within brackets in the Table, was omitted from the calculations of the mean plasma concentration.

BLOOD PRESSURE (Table 2)

The systolic blood pressure decreased significantly

RP/MAP ratio			*Plasma concentration (nmol/l)*				*Blood pressure (mmHg)*			
A	*Ch*	*Ch+A*	*C*	*A*	*Ch*	*Ch+A*	*C*	*A*	*Ch*	*Ch+A*
0·92	0·91	0·92	0	205	0	255	120/80	105/75	120/75	120/75
0·82	0·93	0·84	0	365	0	280	115/75	110/75	115/75	110/70
0·99	0·94	1·12	19	187	(1170)	227	130/80	105/80	100/75	105/75
0·93	0·96	0·79	29	235	134	246	110/80	110/80	110/70	110/70
0·92	0·85	0·93	0	217	0	270	120/75	125/80	110/70	110/70
0·79	0·86	0·88	0	277	0	177	120/80	120/80	120/80	115/75
1·0	0·94	0·98	0	143	0	194	120/75	115/80	125/80	120/85
0·85	1·01	0·98	0	270	0	220	125/70	115/80	130/70	130/80
0·90	0·93	0·93	6	236	19	234	120/77	113/79	116/74	115/75
0·08	0·05	0·10	11	65	50	36	6/4	7/2	10/4	8/5
NS										
			0	236			140/85	125/85		
			0	171			125/70	120/80		
			0	251			135/85	120/90		
			0	311			135/90	125/85		
			0	236			115/85	110/75		
			0	222			120/70	115/90		
			0	256			125/80	120/90		
			0	277			130/90	120/90		
			3	241			124/80	116/82		
			8	53			8/6	7/5		
NS							SBP $p<0·001$			
							DBP NS			

after the injection of metoprolol in untreated volunteers. No other changes were seen. The diastolic blood pressure showed no changes.

SIDE EFFECTS

One volunteer (No. 9) developed right bundle-branch block, which was discovered after the final ventricular effective refractory period determination through the monophasic action potential catheter. The bundle-branch block persisted during four hours of observation after the study but had disappeared one day later.

Discussion

Metoprolol (Seloken®, Hässle läkemedel, Sweden) is a cardioselective beta-adrenergic blocking agent with no intrinsic stimulating activity.[16] It has no local anaesthetic effect at therapeutic dose levels.[16] Its plasma half-life is three to four hours after either a single intravenous or a single oral dose in healthy volunteers. Only 3 per cent of the drug is eliminated unchanged while more than 95 per cent is metabolised in the liver and eliminated in the urine. After oral treatment no detectable amounts of the drug are found in plasma about 40 hours after it has been withdrawn.[16]

In this study, the acute administration of metoprolol had no significant effect on the electrophysiological variables measured from the right ventricle. As expected, heart rate decreased significantly. This is in agreement with the acute electrophysiological effects of other beta-adrenergic blocking agents. During chronic treatment a decrease in heart rate was also seen, reflecting the adaptational bradycardia. Thus, the mean fall in heart rate was seven beats per minute (10%), though healthy young men might not be expected to have much background sympathetic drive. On the other hand, the intravenous dose after chronic treatment produced a further decrease of the heart rate by five beats per minute (8%). Actually, the mean heart rate was almost the same (58 and 56 beats per minute) after acute metoprolol both before and after adaptation, reflecting less response to acute beta-blockade after the adaptation, the mean fall in heart rate being five instead of 10 beats per minute.

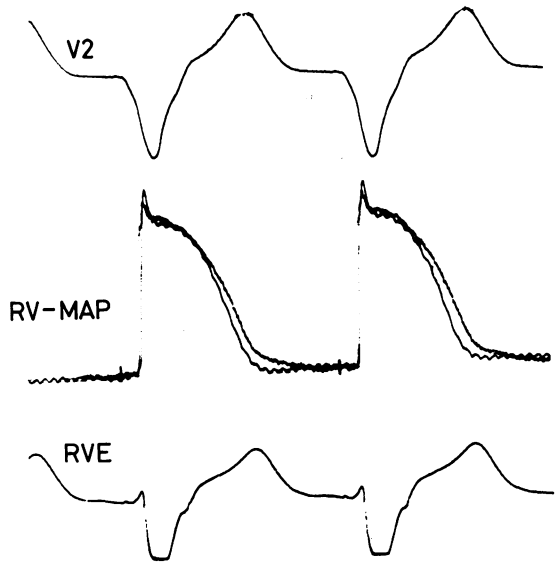

Fig. 3 *The increase of the duration of the right ventricular monophasic action potential (RV-MAP) in one of the subjects (case 3). The MAP signals before and after chronic treatment have been superimposed on each other. Basic stimulation is performed using a stimulus interval of 500 ms. RVE, right ventricular electrogram.*

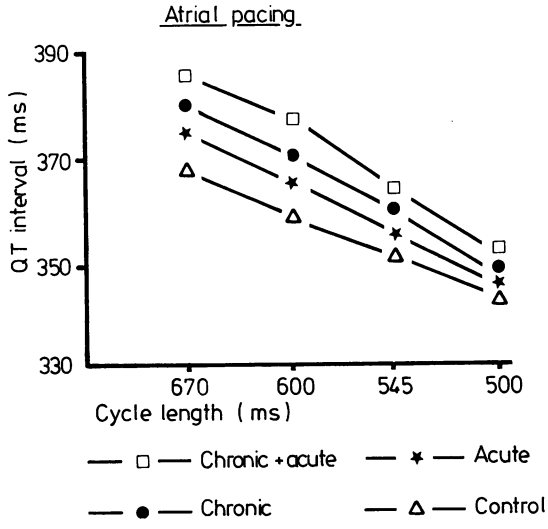

Fig. 4 *QT interval curves after atrial pacing at different stimulation intervals. Acute administration of metoprolol does not produce a significant prolongation of the QT interval in untreated volunteers. Chronic metoprolol treatment prolongs the QT interval significantly at all cycle lengths. An acute injection of metoprolol to chronically treated volunteers also causes a slight prolongation of the QT interval.*

Only one beta-blocker, sotalol, produced prolongation of myocardial action potentials in acute experiments.[17 18] After chronic treatment with metoprolol, however, we found a prolongation of the ventricular repolarisation time. The duration of the repolarisation phase was assessed with three different methods, all showing consistent changes: the right ventricular monophasic action potential duration at 90 per cent repolarisation, the ventricular effective refractory period from the apex and the site of monophasic action potential recording, and finally the QT interval during atrial stimulation.

The QTc, calculated from the Bazett formula, showed slightly different results. Thus, QTc decreased after the injection both in untreated and in chronically treated volunteers. The fact that QTc showed a tendency (though not a significant one) to increase after chronic treatment, when the heart rate was still lower than before treatment, probably reflected an increase of the repolarisation time.

Measurement of the QT interval, however, is often associated with difficulties particularly with defining the end of the T wave, which pathological configuration or the combination of a T and a U wave may obscure.[19] The QT interval is also frequency dependent. The QTc allows a correction corresponding to a heart rate of 60 beats per minute, but this has been shown to give inadequate results in drug studies where atrial stimulation or high physiological heart rates were used.[20] Atrial stimulation, on the other hand, enabled a constant heart rate to be maintained and the QT interval measurements showed changes consistent with those recorded with the other methods used.

It is obvious that the QTc must be used with great caution for the assessment of ventricular repolarisation at different heart rates.[19] The error inherent in the formula may obviously mask the effects observed when heart rate is controlled by atrial pacing[20] and therefore we consider it less suitable for the assessment of variations of ventricular repolarisation than the other three variables, especially since the latter are direct measurements from signals recorded at a constant heart rate.

In this study, the mean monophasic action potential duration increased by 16 ms (6%) after chronic treatment, while the maximal individual increase was 50 ms (22%). The mean increase in the ventricular effective refractory period was 14 ms (6%) at the apex and 19 ms (8%) at the outflow tract, that is of approximately the same magnitude.

These findings may be compared with the results found at atrial level after at least four weeks of oral amiodarone treatment,[21] showing an average increase in monophasic action potential duration of 74

ms (32%). Amiodarone was also found to increase the duration of the action potential of ventricular muscle cells in rabbits in vitro by about 30 per cent.[22]

Among the different components in the specialised conduction system of the heart, the Purkinje fibre cells show the longest repolarisation time under normal conditions. The increase in repolarisation time induced by amiodarone, however, has been shown to affect the atrial and ventricular muscle cells to a greater extent than the Purkinje fibre cells.[23] It would be reasonable to assume that the increase found after chronic treatment with metoprolol using the monophasic action potential technique would also reflect changes in ventricular muscle cell repolarisation rather than in the Purkinje fibre cells, since the monophasic action potential signal consists of signals from a number of cells at the endocardial surface, where the probability of picking up selective signals from the specialised conduction system seems negligible.

The beta-blocker sotalol, long known to cause an increase in action potential duration after acute administration to guinea-pigs in vitro,[17] was recently shown to produce an average increase in the right ventricular monophasic action potential duration of 42 ms (17%) in eight patients with chronic atrial fibrillation receiving a maximum dose of 100 mg intravenously.[24]

This class III mode of action developing during chronic beta-receptor blockade was first shown in rabbit hearts in vitro using a microelectrode technique.[8 9 25] The action potentials of both atria and ventricles increased in duration, especially at the end of the repolarisation. The same phenomenon was seen in vivo in rabbits[25] and in studies in man with QT measurement and QTc calculation.[26] In these studies different beta-blocking agents, both with and without cardioselectivity and intrinsic stimulating activity, were used. This suggests that the increase in repolarisation time may be a general property of beta-blockers, regardless of their pharmacological differences.

The effect of chronic beta-receptor blockade upon ventricular repolarisation is in strong contrast to the lack of influence on ventricular repolarisation which characterises acute beta-blockade, the only exception being sotalol, which has a pronounced class III action after acute administration in animal experiments in vitro[17 18] and in man.[24]

The subtle changes of the ventricular repolarisation that we have noted are within the range of inter-individual differences noted in a population of healthy subjects.[26] The possible connection between changes in ventricular repolarisation and the antiarrhythmic effects of chronic beta-receptor blockade must be made with great caution. For instance, it must still be considered an open question whether the lower mortality in patients who are treated with beta-blockers after acute myocardial infarction[27 28] can be related to a decreased susceptibility to life-threatening ventricular arrhythmias on the basis of this very moderate prolongation of the ventricular repolarisation, a mechanism that has been suggested.[9 25]

References

1 Vaughan Williams EM. Classification of antiarrhythmic drugs. In: Sandoe E, Flenstad-Jensen E, Olesen KH, eds. *Symposium on cardiac arrhythmias.* Södertälje: Astra, 1970: 449–69.

2 Wit AL, Hoffman BF, Rosen MR. Electrophysiology and pharmacology of cardiac arrhythmias IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade. Part C. *Am Heart J* 1975; **90:** 795–803.

3 Seides SF, Josephson ME, Batsford WP, Weisfogel GM, Lau SH, Damato AN. The electrophysiology of propranolol in man. *Am Heart J* 1974; **88:** 733–41.

4 Berkowitz WD, Wit AL, Lau SH, Steiner C, Damato AN. The effects of propranolol on cardiac conduction. *Circulation* 1969; **40:** 855–62.

5 Prichard BNC. The use of beta adrenergic blocking drugs in cardiovascular disease. *Scott Med J* 1976; **21:** 182–7.

6 Fitzgerald JD. Beta blocking drugs as antiarrhythmic agents. *Int J Clin Pharmacol Biopharm* 1975; **11:** 235–44.

7 Singh BN, Jewitt DE. β-adrenergic receptor blocking drugs in cardiac arrhythmias. *Drugs* 1974; **7:** 426–61.

8 Vaughan Williams EM, Raine AEG, Cabrera AA, Whyte JM. The effects of prolonged β-adrenoceptor blockade on heart weight and cardiac intracellular potentials in rabbits. *Cardiovasc Res* 1975; **9:** 579–92.

9 Raine AEG, Vaughan Williams EM. Possible explanation for protective action of long-term beta-adrenoceptor blockade after myocardial infarction (abstract). *Br Heart J* 1976; **38:** 873–4.

10 Harper RW, Olsson SB. Effect of mexiletine on conduction of premature ventricular beats in man. *Cardiovasc Res* 1979; **13:** 311–9.

11 Olsson SB. *Monophasic action potentials of right heart.* Göteborg: Elanders Boktryckeri AB, 1971.

12 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1918–1920; **7:** 353–70.

13 Rydén L, Olsson B, Kvasnička J. Electrophysiological effects of the antiarrhythmic agent QX-572 in the human heart with special reference to rate-induced changes in effective refractory periods. *Cardiovasc Res* 1975; **9:** 81–94.

14 Olsson SB, Brorson L, Harper R, Rydén L. Estimation of ventricular refractoriness in man by the extra stimulus method. *Cardiovasc Res* 1977; **11:** 31–8.

15 Guss SB, Kastor JA, Josephson ME, Scharf DL. Human ventricular refractoriness: effects of cycle

length, pacing site and atropine. *Circulation* 1976; **53:** 450–5.
16 Åblad B, Borg KO, Carlsson E, Ek L, Johnsson G, Malmfors T, Regårdh C-G. A survey of the pharmacological properties of metoprolol in animals and man. *Acta Pharmacol Toxicol (Kbh)* 1975; **36,** suppl 5: 7–23.
17 Strauss HC, Bigger JT Jr, Hoffman BF. Electrophysiological and beta receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue. *Circ Res* 1970; **26:** 661–78.
18 Singh BN, Vaughan Williams EM. A third class of antiarrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. *Br J Pharmacol* 1970; **39:** 675–87.
19 Fredlund BO, Olsson SB. Mätning av Q-T-tid, svårigheter, variabilitet, normalvärden och effekt av arbete. *Acta Societatis Medicorum Suecanae* 1978; **87:** part 3: 110.
20 Milne J, Ward D, Camm J, Spurrell R. The effect of propranolol on the QT and QTc intervals assessed by atrial pacing. *Trans Eur Soc Cardiol* I No 1 1978:57.
21 Olsson SB, Brorson L, Varnauskas E. Class 3 antiarrhythmic action in man. Observations from monophasic action potential recordings and amiodarone treatment. *Br Heart J* 1973; **35:** 1255–9.
22 Singh BN, Vaughan Williams EM. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol* 1970; **39:** 657–67.
23 Rosenbaum MB, Chiale PA, Halpern MS, *et al.* Clinical efficacy of amiodarone as an antiarrhythmic agent. *Am J Cardiol* 1976; **38:** 934–44.
24 Edvardsson E, Hirsch I, Emanuelsson H, Pontén J, Olsson SB. Sotalol-induced delayed ventricular repolarization in man. *Eur Heart J* 1980; **1:** 335-43.
25 Raine AEG, Vaughan Williams EM. Electrophysiological basis for the contrasting prophylactic efficacy of acute and prolonged beta-blockade. *Br Heart J* 1978; **40,** suppl: 71–7.
26 Edvardsson N, Olsson SB. Right ventricular monophasic action potentials in healthy young men. To be published.
27 Wilhelmsson C, Vedin JA, Wilhelmsen L, Tibblin G, Werkö L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 1974; **ii:** 1157–60.
28 Multicentre International Study. Improvement in prognosis of myocardial infarction by long-term beta adrenoceptor blockade using practolol. *Br Med J* 1975; **iii:** 735–40.

Requests for reprints to Dr Nils Edvardsson, Department of Cardiology, Medical Clinic I, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.